IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Jeffery I. WEITZ — Examiner: Leigh C. MAIER

Serial No.: 10/019,325 — Group Art Unit: 1623

Filed: February 27, 2002

Title: HEPARIN COMPOSITIONS THAT INHIBIT CLOT ASSOCIATED COAGULATION FACTORS

DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Jeffrey I. Weitz, being duly warned, declare as follows.

2. I am a coinventor in the above-identified application. I do not have a financial interest in this application.

3. My CV is attached, demonstrating my expertise to make the statements in this declaration.

4. I have read the above-identified application, the office action of January 14, 2004 and the references cited therein, i.e., EP 101141 (Hepar) and EP 244235 (Nielsen).

5. The following facts establish that neither of these references discloses or suggests experiments which produce medium molecular weight heparin (MMWH) of this invention having molecular weights (weight average) in the range of 6,000 to 12,000 Daltons wherein at least 15% of the sulfated oligosaccharides have at least one pentasaccharide sequence. Moreover, no part of the disclosures of these references suggests controlling the experimental

procedures to prepare a heparin having, for example, this 15% pentasaccharide sequence property.

6. Standard heparin has a number average molecular weight of about 12,000 Daltons with a range of 11,200 to 11,900 Daltons depending on the method of analysis and the heparin preparation (Barlow GH, et al. *Arch Biochem* 1961;84:518-525; Lasker SE and Stivala SS, *Arch Biochem* 1966;115:360-372; Laurent, et al. *Biochem J* 1978;175:691-701). As noted in the specification of the above-identified application, "The interaction of heparin with antithrombin is mediated by a unique pentasaccharide sequence that is randomly distributed on about one-third of the heparin chains." (page 1, lines 11 – 13). See also, e.g., page 9, lines 14-36 of the above-identified application for a discussion of this pentasaccharide feature. However, there are problems associated with standard heparin having this desirable pentasaccharide sequence, as discussed on pages 1 and 2 of the specification. To alleviate these, this invention lowers the molecular weight of the heparin by shortening the average chain length of the oligosaccharides, e.g., to a weight average molecular weight of 6,000 to 12,000 Daltons. (Page 7, lines 36-38; page 12, lines 32-33; etc.). It has been discovered that the corresponding heparin chains of this invention advantagely are too short to bridge thrombin to fibrin, but are of sufficient length to bridge antithrombin to thrombin. Thus, the compositions of this invention inactivate both fibrin-bound thrombin and free thrombin. (Page 8, lines 27-35, etc.)

7. Applicant's specification discloses several methods to depolymerize heparin in order to achieve both the desired lower molecular weight and the desired retained pentasaccharide content. These include nitrous acid treatment (page 11, line 15 - page 13, line 3), enzymatic depolymerization by heparinase (page 13, lines 4-14) and limited periodate oxidation/hydrolysis (page 13, lines 15 - page 14, line 2). In all cases, sufficient conditions and controls are utilized to achieve the parameters defining the invention.

8. Nielsen employs a heparinase depolymerization to achieve various fractions of heparin having stated molecular weights. The highest number average molecular weight reported in Nielsen is 4900 (Table II) for fraction 10. The latter also has the highest weight average

molecular weight (8800). This highest molecular weight fraction (and necessarily all lower molecular weight fractions reported in Neilsen) has a pentasaccharide content less than 15%. As noted in paragraph 6 above, one third of the chains in standard heparin have the desired pentasaccharide sequence. Given the standard heparin number average molecular weight of 12,000, it can be seen that a heparinase-treated standard heparin having a number average molecular weight of 4,900 has only (4,900/12,000) X 33.3% of the desired pentasaccharide sequences. Thus, there are less than 13.6% of such sequences remaining in the resultant highest pentasaccharide-content fraction of Nielsen.

9. Whereas Nielsen generally discusses the control of its depolymerization reaction in order to achieve a desired molecular weight range, Nielsen does not suggest that any molecular weights higher than those reported in its tables should be sought. Just the opposite conclusion would be drawn from Neilsen. At the bottom of page 1 of Neilsen is a stated preference for heparin fractions having high factor Xa activity. As noted at the bottom of page 2 of the above-identified application, low molecular weight heparins have significantly more antifactor Xa activity than anti-factor IIa activity. More generally, it is well known that lower molecular weight chains in a heparin sample (e.g., less than 8000 Daltons (weight average)) have higher anti-factor Xa activity than do higher chains (Barrowcliffe TW, et al. *J Pharm Biomed Anal* 1989;7:217-226; Bray B, et al. *Biochem J* 1989;262:225-232). Thus, there is nothing that an ordinarily skilled worker could find in Nielsen encouraging production of any molecular weights higher than the highest reported in its tables. Similarly, there is no mention in Neilsen of retaining the pentasaccharide subunit in the heparin chains as required by this invention.

10. Hepar also relates to the depolymerization of heparin. This reference discloses a general range of 4,000 to 12,000 Daltons. There is no discussion of any aspect which would lead an ordinarily skilled worker to choose a lower limit on the molecular weight of 6,000 as recited for this invention. The latter "was specifically chosen to ensure that all of the heparin chains of the MMWH compositions are of a sufficient length to bridge anti-thrombin to thrombin regardless of where the pentasacchride sequence is located within the heparin chains." (page 2,

lines 14 – 16)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Name

Oct 13/04

Date

CURRICULUM VITAE

NAME:	Jeffrey Ian Weitz
ADDRESS:	54 Carluke Road East Ancaster, Ontario L9G 3L1 (905)648-4506
BUSINESS ADDRESS:	Henderson Research Centre 711 Concession Street Hamilton, Ontario L8V 1C3
TELEPHONE:	(905) 574-8550
FAX:	(905) 575-2646
DATE OF BIRTH:	October 14, 1952
MARITAL STATUS:	Married, 2 children
CITIZENSHIP:	Canadian

CURRENT TITLES AND POSITIONS:

Professor of Medicine and Biochemistry, McMaster University
Director, Henderson Research Centre
Director, Experimental Thrombosis & Atherosclerosis Group, Henderson Research Centre
Canada Research Chair (Tier 1) in Thrombosis
HSFO/J. Fraser Mustard Chair in Cardiovascular Research
Career Investigator, Heart and Stroke Foundation of Canada

QUALIFICATIONS:

University of Ottawa, Ottawa, Ontario	Honours Biology	1970-1972
University of Ottawa, Ottawa, Ontario	M.D., Magna Cum Laude	1972-1976

CERTIFICATION:

Fellow, Royal College of Physicians (Canada)	1980
Diplomate, American Board of Internal Medicine	1980
Diplomate, American Board of Medical Oncology	1981
Diplomate, American Board of Hematology	1982
Fellow, American College of Physicians	1988
Fellow, Council on Arteriosclerosis, Thrombosis & Vascular Biology	1997
Fellow, American College of Chest Physicians	2000
Fellow, American Heart Association	2002

HOSPITAL TRAINING AND POSITIONS:

Intern, Internal Medicine, Toronto General Hospital	1976-1977
Resident, Internal Medicine, Toronto General Hospital	1977-1978
Fellow, Hematology-Oncology, Toronto General Hospital	1978-1980
Research Fellow, Hematology-Oncology, Columbia University, College of Physicians & Surgeons, New York, NY	1980-1982
Instructor of Medicine, Columbia University, College of Physicians & Surgeons, New York, NY	1982-1983
Assistant Physician, Columbia Presbyterian Medical Center, New York, NY	1982-1983
Assistant Professor of Medicine, Columbia University, College of Physicians & Surgeons, New York, NY	1983-1986
Assistant Attending Physician, Columbia Presbyterian Medical Center, New York, NY	1983-1986
Associate Director, Coagulation Laboratory, Columbia Presbyterian Medical Center, New York, NY	1983-1986
Assistant Professor of Medicine, McMaster University, Hamilton, Ontario	1986-1988
Associate Professor of Medicine, McMaster University, Hamilton, Ontario	1988-1992
Professor of Medicine, McMaster University, Hamilton, Ontario	1992-present
Active Staff, Hamilton Health Sciences (formerly Hamilton Civic Hospitals)	1986-present
Consultant, Hamilton Regional Cancer Centre	1986-present
Director, Thromboembolism Unit, Henderson General Hospital	1989-2000
Director, Division of Thromboembolism, Hamilton Civic Hospitals	1991-2000
Acting Head of Basic Research, Hamilton Regional Cancer Centre	1992-1994
Director, Experimental Thrombosis and Atherosclerosis Group, Henderson Research Centre	1993-present
Associate Director, Hamilton Civic Hospitals Research Centre	1999-2003
Director, Henderson Research Centre	2003
Professor of Biochemistry, McMaster University	2003

HONOURS:

Engineers Association Scholarship	1971
Dean's Honour List	1971-72
Ontario Heart Foundation Student Scholarship	1974
New York Heart Association Research Scholarship	1984-86
Heart & Stroke Foundation of Ontario Scholarship Award	1987-92
Listing, Who's Who in Canada	1989-present
Medal in Medicine, Royal College of Physicians and Surgeons (Canada)	1991
Heart and Stroke Foundation of Ontario Career Investigator Award	1992-2007
Fellow, Council on Arteriosclerosis, Thrombosis, and Vascular Biology	1997
Medical Research Council of Canada Scientist Award	. . . Declined

Distinguished Scientist Award, Heart & Stroke Foundation of Ontario	1999
Heart & Stroke Foundation of Ontario/J. Fraser Mustard Chair in Cardiovascular Research	2000-present
Canada Research Chair in Thrombosis (Tier 1)	2001-present
Nationwide Register's Who's Who in Executives and Business	2001-present
Fellow, American Heart Association	2001
Fellow, American College of Chest Physicians	2002
Honored Member, Heritage Registry, Who's Who	2004
Fellow, Society of Vascular Medicine and Biology	2004

PROFESSIONAL ORGANIZATIONS:
Elected Membership:

American Society for Biochemistry and Molecular Biology
Canadian Society of Hematology
American Society of Hematology
American College of Physicians
American Society of Clinical Oncology
American Association for the Advancement of Science
American Society for Clinical Investigation
American Heart Association
New York Academy of Science
International Society of Thrombosis and Haemostasis
Advisory Committee, New York Chapter, National Hemophilia Foundation
American Federation for Clinical Research
Canadian Society of Clinical Investigation
Canadian Institute of Academic Medicine
American Chemical Society
Canadian Cardiovascular Society

Non-elected Membership:

Royal College of Physicians and Surgeons (Canada)
Ontario Medical Association
College of Physicians and Surgeons of Ontario

PROFESSIONAL ACTIVITIES:
Journal Referee:

New England Journal of Medicine
Lancet
Biochemistry

Journal of Biological Chemistry
Journal of Clinical Investigation
Blood
Thrombosis and Haemostasis
Annals of Internal Medicine
American Review of Respiratory Diseases
Arteriosclerosis, Thrombosis, and Vascular Biology
Clinical and Investigative Medicine
Circulation
Thrombosis Research
Journal of Laboratory and Clinical Medicine
Proceedings National Academy of Sciences (USA)
Journal of Thrombosis and Haemostasis
Journal of the American Medical Association (JAMA)

Grant Committees:

Medical Research Council (Experimental Medicine)	1989-1991
Medical Research Council (Cardiovascular "A")	1992-1997
Heart and Stroke Foundation of Canada, Committee V	1993-1994
Heart and Stroke Foundation of Ontario, Research & Development Committee	1989-1995

EXECUTIVE POSITIONS:

Member, Executive Council, American Heart Association Council on Thrombosis	1991-1993
Vice-Chair, Research and Development Committee, HSFO	1992-1993
Chair, Research & Development Committee, Heart & Stroke Foundation of Ontario	1994
Member, American Society for Clinical Investigation	1993-present
Vice-President, Research, Heart and Stroke Foundation of Ontario	1995-1997
Chair, Research &Development Committee, HSFO	1994-1995
Member, Research Policy Committee, Heart & Stroke Fdn of Ont.	1992-1995
Member, Nominating Committee, Heart & Stroke Fdn of Ontario	1995-1997
Chair, Research Policy Committee, Heart & Stroke Fdn. of Ont.	1995-1997
Member, Stroke Task Force, Heart and Stroke Foundation of Ontario	1993-1995
Member, Medical Advisory Committee, Heart & Stroke Fdn. of Canada	1995-1997
Scientific Officer, Cardiovascular A Grant Review Committee, Medical Research Council of Canada	1994
Assembly delegate, American Heart Association, Council on Thrombosis	1994-1996
Member, Board of Directors, Heart & Stroke Fdn. of Ont.	1994-2003

Director, Cardiovascular Research, Vascular Therapeutics, Inc., Mountainview, California	1995-1999
Member, Committee on Vascular Biology, American Society of Hematology	1996-2001
Deputy Chair, Scientific Review Committee, Heart & Stroke Fdn. of Canada	1997-1998
Deputy Chair, Committee IX (Senior Personnel), Heart & Stroke Foundation of Canada	1997-1998
Institutional Representative, American Society for Clinical Investigation	1997-present
Chair, Scientific Review Committee, Heart & Stroke Foundation of Canada	1998-2000
Chair, Committee IX (Senior Personnel), Heart & Stroke Foundation of Canada	1998-2000
Member, Editorial Board, Arteriosclerosis, Thrombosis and Vascular Biology	1999-2008
Chair, Committee on Vascular Biology and Thrombosis, American Society of Hematology	1999-2001
Member, Educational Committee, American Society of Hematology	1999-2004
Director, Cardiovascular Research, GlycoDesign, Inc., Toronto, Ontario	1999-2003
Member, Editorial Board, Journal of Thrombosis and Thrombolysis	2000-2002
Member, Editorial Board, Current Drug Targets – Cardiovascular & Haematological Disorders	2000-2002
Member, Editorial Board, *Haemostasis Forum*	2003-present
Member, Editorial Board, *Thrombosis and Haemostasis*	2002-2004
Chair, Research Policy Committee, Heart &Stroke Foundation of Ontario	2002-2004
Member, Research Policy and Planning Advisory Committee, Heart & Stroke Foundation of Canada	2001-2003
Member, Editoral Board, *The Canadian Journal of Cardiology*	2003-2006
Member, Editorial Board, *Current Cardiology Reviews*	2005

External Grant Reviews:

Medical Research Council of Canada
Canadian Institutes of Health Research
Heart and Stroke Foundation
Canadian Red Cross/Canadian Blood Services
Veterans' Administration (United States)
National Institutes of Health (United States)
Wellcome Trust (United Kingdom)

Internal Grant Reviews:

Bickle Foundation

AREAS OF INTEREST:

(a) RESEARCH: Biochemistry of coagulation and fibrinolysis and the application of basic data to the study of clinically relevant problems in thrombosis, hemostasis, and inflammation
(b) CLINICAL: Management of patients with thrombotic and hemorrhagic disorders
(c) TEACHING: Integration of basic research concepts into the practice of evidence-based medicine

COURSES TAUGHT (in past 5 years):

Undergraduate:

Coordinator, Clinical Skills Laboratory (Hematology)	1986-1988
Lecturer, venous thromboembolic disease (Unit III)	1987-1988
hematology review (Unit VI)	1987-2001
Clinical Skills Preceptor (Unit III)	1987-1990
Student Advisor (Laura Kelly, Karin Wollschlaeger, Andrew Viera, Diane Wong, Rosalind Ward-Smith, Saramina Wingate, Elena Ostapenko, Aleksa Cenic, Connie Taylor, Natalie Baine, Talya Wise)	1986-present
Resource person (Units III and V)	1986-present

Graduate:

Lecturer and Unit Coordinator (MS732): Vascular Diseases, Hemostasis and Thrombosis

Supervisorships:
Post-doctoral

Dr. M. Cruickshank	April 1987 - July 1987
Dr. J. Ginsberg	July 1987 - June 1988
Dr. J. Kuint	July 1987 - June 1988
Dr. D. Massel	January 1989 - June 1990
Dr. D. Anderson	November 1989 - July 1991
Dr. M. Prins	November 1989 - July 1991
Dr. J. Vogel	July 1990 - July 1991
Dr. B. Cosmi	July 1991 - June 1993
Dr. J. Fredenburgh	July 1993 - July 1996
Dr. J. Anderson	July 1997 - June 1999

Dr. A. Lee	July 1996 - June 2000
Dr. S. Bates	July 1996 - June 2000
Dr. A. Dua	July 2002 - present

Doctoral:

Dr. P. Klement	completed 1994
Dr. P. Liaw	completed 1999
Dr. R. Stewart	completed 2000
Mr. H. Al Shurafa	in progress

Masters:

Debra Becker	completed 1997
Amy Lazier	completed 2000
Lee O'Brien	completed 2001
Ericka Wiebe	completed 2001
Michelle Szrajber	completed 2002
Caroline Pospisil	completed 2003
Long Tieu	completed 2004
Teresa Lim	completed 2004
Colin Kretz	In progress

Thesis Committee Member:

M.Sc.:	Anita Borm	(completed 1990)
	Paresh Patel	(completed 1990)
	Fraser Rubens	(completed 1992)
	Benilde Cosmi	(completed 1993)
	Denise Foulon	(completed 1995)
	Dave Singh	(completed 1995)
	Gary Skarja	(completed 1995)
	Andrew Outinen	(completed 1997)
	Aimee Mabini	(completed 1997)
	Debra Becker	(completed 1998)
	Vivian Douros	(completed 1999)
Ph.D.:	Kimberly Woodhouse	(completed 1993)
	Yuan Tian	(completed 1995)
	Ying Jun Du	(completed 2001)

Bryan Wickson	(in progress)
Kimberley Walton	(in progress)

ADMINISTRATIVE RESPONSIBILITIES:

(a) Hospital:	
Research Ethics Board, Hamilton Health Sciences	1988-present
Executive Committee, Dept. of Medicine, Hamilton Civic Hospitals	1990-present
Director, Thromboembolism Unit, Henderson Hospital	1989-1999
Head, Division of Thromboembolism, Hamilton Civic Hospitals	1991-2000
Acting Head of Basic Research, Hamilton Regional Cancer Centre	1992-1994
Director, Experimental Thrombosis and Atherosclerosis Group	1993-present
(b) University:	
Advisory Committee for Hematology	1986-present
M.D. Admissions Collation Committee	1989-1993
Research Committee, Dept. of Medicine (Chairman as of 1991)	1990-present
Executive Committee, Dept. of Medicine	1991-present
Promotion and Tenure Committee, Dept. of Medicine	1992-present
(c) Faculty:	
Facilitating Committee, Faculty of Health Sciences	1991-present
Research Cabinet, Faculty of Health Sciences	2002-present

Invited Presentations:

1. Phelps Memorial Hospital, New York, NY. Hereditary disorders of coagulation, Feb. 22, 1985.
2. Columbia University, New York, NY. Hematology review, March 4, 1985.
3. State University of New York, Stony Brook, NY. Development and applications of an assay for in vivo neutrophil elastase activity, April 12, 1985.
4. Merck, Sharp and Dohme Research Laboratories, Rahway, NJ. Development of an assay for in vivo neutrophil elastase activity, July 8, 1985.
5. Washington University, St. Louis, MO. Clinical applications of an assay for neutrophil elastase activity, September 30, 1985.
6. National Institutes of Health, Bethesda, MD. Potential applications of an assay for neutrophil elastase activity, January 27, 1986.
7. Case Western Reserve University, Cleveland, OH. Role of neutrophil elastase in health and disease, February 13, 1986.

8. Columbia University, New York, NY. Internal Medicine Board Review Course, March 3, 1986.
9. National Institutes of Health, Bethesda, MD. Effects of cigarette smoking on neutrophil elastase activity, May 30, 1986.
10. New York Internal Medicine Board Review Course, New York, NY. Platelets and coagulation, July 12, 1986.
11. Stuart Pharmaceuticals, Wilmington, DE. Development and applications of an assay to neutrophil elastase activity, September 17, 1986.
12. Mohawk College, Hamilton, Ont. Biochemical markers of thrombosis, October 25, 1986.
13. McMaster University, Hamilton, Ont. Coagulation, platelets and thrombolysis in cardiovascular disease, November 4, 1986.
14. Stuart Pharmaceuticals, Wilmington, DE. Utility of an assay for neutrophil elastase activity in monitoring the response to elastase inhibitors, June 24, 1987.
15. New York Blood Center, New York, NY. Basic and clinical applications of an assay for neutrophil elastase activity, October 8, 1987.
16. New York Academy of Sciences, New York, NY. Clinical monitoring of elastase activity, October 15, 1987.
17. Abbott Research Laboratories, Chicago, ILL. Novel activities of the endogenous plasminogen activators, January 15, 1988.
18. Queen's University, Kingston, Ont. Plasminogen activator-mediated fibrinopeptide release, February 1, 1988.
19. Greater Niagara Falls General Hospital, Niagara Falls, Ont. Selected aspects of coagulation, March 18, 1988.
20. Mohawk College, Hamilton, Ont. Low molecular weight heparins, March 9, 1988.
21. Gordon Research Conference, Plymouth, NH. Clinical and basic applications for an assay of neutrophil elastase activity, June 15, 1988.
22. American Association of Clinical Chemists, New Orleans, LA. Clinical utility of monitoring intravascular coagulation and fibrinolysis, July 28, 1988.
23. Royal College of Physicians and Surgeons, Ottawa, Ont. Biochemical diagnosis of the hypercoagulable state, September 24, 1988.
24. Centocor Corp., Malvern, PA. Clinical utility of assays for fibrinopeptides, September 28, 1988.
25. Temple University, Philadelphia, PA. Role of neutrophil elastase in health and disease, October 18, 1988.
26. Tele-medicine, Toronto, Ont. Fibrinolysis, October 27, 1988.
27. American Heart Association, Washington, DC. Sensitivity and specificity of assays for in vivo thrombin activity, November 16, 1988.
28. Biogen Inc., Boston, MA. Potential mechanisms by which the clot can influence the results of thrombolytic therapy, December 1, 1988.

29. Ottawa Heart Institute, Ottawa, Ont. Monitoring activation of platelets and coagulation in patients with Ventricular Assist Devices, March 3, 1989.
30. Temple University, Philadelphia, PA. Hemostasis update: Intravascular Coag., Apr.13, 1989.
31. DuPont Pharmaceuticals, Wilmington, DE. Clot-associated thrombin is protected from heparin inhibition, May 19, 1989.
32. Gordon Research Conferences, NH. Elastase-derived fibrinopeptides, August 8, 1989.
33. Mohawk College, Hamilton, Ont. Inhibitors of thrombin and plasmin, October 30, 1989.
34. American Society of Hematology, Atlanta, GA. Mechanism of t-PA induced fibrinogenolysis. December 2,3, 1989.
35. University of Vermont, VT. Plasminogen activators have direct catalytic activity against fibrinogen, December 14, 1989.
36. New York Academy of Sciences, Orlando, FL. Development and application of assays for elastase-specific fibrinopeptides. May 10, 1990.
37. University of Michigan, Ann Arbor, MI. Limitations of heparin therapy. Why t-PA is not clot-specific. June 25, 1990.
38. University of Toronto, Toronto, Ont. Development and application of assays for elastase-derived fibrinopeptides. October 10, 1990.
39. American College of Chest Physicians, Toronto, Ont. Mechanism of action of thrombolytic agents. October 22, 1990.
40. McGill University, Montreal, Quebec. Why t-PA is not clot-specific. February 15, 1991.
41. American College of Cardiology, Atlanta, GA. Biochemical markers of thrombosis. March 1, 1991.
42. Cleveland Clinic Research Foundation, Cleveland, OH. The potential clinical importance of clot-bound thrombin. September 16, 1991.
43. American College of Cardiology, Dallas, TX. New concepts in the therapeutic actions of heparin. April 15, 1992.
44. Restenosis Summit, Cleveland, OH. Thrombin inhibitors, potential role in restenosis. May 29, 1992.
45. Mt. Sinai Hospital, Toronto, Ont. Update in Family Practice: ASA. September 27, 1992.
46. Lehigh Valley Hospital, Allentown, PA. Coagulation Symposium. Unfractionated and low molecular weight heparins. October 2, 1992.
47. University of Connecticut and American Red Cross, Harford, CT. Transfusion 2001: New Antithrombins. October 8, 1992.
48. Maine Medical Center, Portland, Maine. Medical Grand Rounds. New Anticoagulant Strategies. March 3, 1993.
49. University of Minnesota, Minneapolis, MN. Blood Club. Potential mechanisms of tissue plasminogen activator-induced fibrinogenolysis and bleeding. October 28, 1993.

50. University of Minnesota, Minneapolis, MN. Mayo Clinic. New antithrombotic strategies. October 30, 1993.
51. Thrombolysis Gordon Conference, Ventura, CA. Discussion leader and invited speaker. New approaches to thrombolysis. March 13-18, 1994.
52. North Shore University Hospital , Manhasset, NY. Seventh Annual Lectures in Contemporary Hemostasis and Thrombosis. Clinical Use of Low Molecular Weight Heparins. June 24, 1994.
53. American College of Chest Physicians, New Orleans, LA. Low molecular weight heparins. Biochemistry and Pharmacology. November 1, 1994.
54. American Heart Association, Dallas, TX. (a) Plenary Session - Thrombin and its inhibitors, Nov. 16, 1994. (b) Postgraduate symposium-Low molecular weight heparin. Biochemistry, Nov. 16, 1994.
55. American Society of Hematology, Nashville, TN. Educational sessions: Low molecular weight heparins, December 3-4, 1994.
56. Antithrombotic Therapy Consensus Conference, Tucson, AZ. Percutaneous transluminal coronary angioplasty and antithrombotic therapy, March 30 - April 2, 1995.
57. Thrombolysis Summit Meeting, Snowbird, UT. The promise of thrombin inhibitors and platelet inhibitors, April 6-9, 1995.
58. National Antithrombin Investigator's Meeting, Naples, FL. Low molecular weight heparin, May 18-22, 1995.
59. Anticoagulant, Antithrombotic, and Thrombolytic Therapies Conference, Washington, DC. Limited fibrin specificity of tissue-type plasminogen activator and its potential link to bleeding, October 23-25, 1995.
60. Hemostasis and Thrombosis Second Annual Symposium, Summit, NJ. Management of deep vein thrombosis, October 31, 1995.
61. American Society of Hematology, Seattle, WA. Thrombosis. December 1-5, 1995.
62. American College of Physicians - Hematology MKSAP 2 Committee, Philadelphia, PA. March 12-13, 1996.
63. International Symposium on the Chemistry and Biology of Serpins Meeting, Chapel Hill, North Carolina. Antithrombin III- and heparin cofactor II-mediated inhibition of fluid-phase and clot-bound thrombin. April 13-16, 1996.
64. Hemostasis and Thrombosis Update, 1996, Philadelphia, PA. Markers of thrombin generation and action. April 25-27, 1996
65. The Seventh Annual Meeting of the Society for Vascular Medicine and Biology, Chicago, Illinois. Low molecular weight heparins for the out-of-hospital management of patients with venous thromboembolic disease. June 8-9, 1996.
66. Gordon Conference, Andover, New Hampshire. Studies on the mechanisms by which fibrin monomer protects thrombin from inactivation by heparin-serpin complexes. June 9-14, 1996.

67. XVIIIth Congress of the European Society of Cardiology, Birmingham, UK. New antithrombotic strategies. August 25-29, 1996.
68. Visiting Professor, Departments of Pathology and Biochemistry, University of British Columbia, British Columbia. April 23-25, 1997.
69. Visiting Professor, University of Michigan, Ann Arbor, MI. May 8-9, 1997.
70. CME Talk - Cardiology Program, Sheraton Hotel, Hamilton, Ontario. Antithrombotic Therapy for Atrial Fibrillation. May 14, 1997.
71. Cancer Medicine and Hematology, Boston, MA. Anticoagulant Therapy. September 24-25, 1997.
72. Midwest Blood Clinic, Chicago, IL. Lessons from the vampire bat -- a more fibrin-selective plasminogen activator. September 25, 1997.
73. Hirulog Advisory Board Meeting, Cleveland, OH. October 20-21, 1997.
74. Winthrop University Hospital Advances in Medicine Program, Long Island, NY. Use of low molecular weight heparins. October 22, 1997.
75. AHA Hirulog Experts Meeting, Orlando, FL. Mechanism of Action. November 8, 1997.
76. American Heart Association Meeting, Orlando, FL. Vasoflux, a novel anticoagulant that is more effective than heparin and safer than hirudin in rabbits. November 9-12, 1997.
77. American Society of Hematology, San Diego, CA. Vasoflux, a novel anticoagulant that is more effective than heparin and safer than hirudin in rabbits. December 5-9, 1997.
78. Hirulog Advisory Board Meeting, Expert's Symposium, Atlanta, GA. Mechanism of action -- New and Current Therapies. March 27-29, 1998.
79. American College of Chest Physicians, 5th Consensus Conference, Tucson, Arizona. New Antithrombins. April 17-19, 1998.
80. Coalition for Internal Medicine Meeting, Hershey, PA. Low molecular weight heparins, May 1-3, 1998.
81. Cambridge Healthtech Institute, San Diego, CA. New Antithrombotic Strategies, May 27-29, 1998.
82. Pacific Rim Summit on Vascular Medicine, San Diego, CA. Low molecular weight heparins, heparinoids, and the outpatient treatment of venous thromboembolic disease, June 5-6, 1998.
83. Long Term antithrombotic treatment in post-MI patients: The old and new, New York, NY. Mechanism of action of oral antithrombotic drugs, June 11-14, 1998.
84. XX Annual Meeting of the International Society for Heart Research, Ann Arbor, MI. Vasoflux, a new anticoagulant with a novel mechanism of action, August 9-12, 1998.
85. European Society of Cardiology Satellite Symposium, Vienna, Austria. Mechanism of action -- New and current therapies. August 19-26, 1998.
86. Global Approaches to Treating Vascular Disease, Toronto, Ontario. The role of platelets in cardiovascular disease. September 25-26, 1998.

87. London Cardiovascular Society, London, Ontario. Visiting Professor. Vampire bat plasminogen activator: (?Draculytic therapy). October 1, 1998.
88. Canadian Cardiovascular Society Meeting - Satellite Symposium, Ottawa, Ontario. Platelet inhibitors in cardiology: from aspirin to GPIIb/IIIa's. October 20, 1998.
89. Illinois Masonic Medical Center in Oakbrook Symposium, Oakbrook, Illinois. Low-molecular-weight heparins; changing the way we treat thrombosis. October 28, 1998.
90. American Heart Association, Dallas, Texas. V20, a glycoprotein IIb/IIIa-independent inhibitor. November 6-11, 1998.
91. American Heart Association- Hirulog Advisory Board Meeting, Dallas, Texas. Direct thrombin inhibition: New approaches to anticoagulation. November 7, 1998.
92. Clinical Implications Beyond MI, Niagara-on-the-Lake, Ontario. November 13-14, 1998.
93. Canadian Heart Research Centre Symposium, Toronto, Ontario. Low molecular weight heparin (LMWH). November 27-29, 1998.
94. American Society of Hematology, Miami, Florida. Thrombosis III: new antithrombotic agents. December 5-9, 1998.
95. Canadian Society for Clinical Investigation, Montreal, Quebec. February 12-17, 1999.
96. Cardiology Grand Rounds, Montreal, Quebec. Montreal General Hospital. February 16, 1999.
97. Grand Rounds, Royal Victoria Hospital, Montreal, Quebec. February 17, 1999.
98. University of Montreal, Montreal, Quebec - LMWH in acute coronary syndromes. April 9-10, 1999.
99. St. Boniface General Hospital Research Centre, Winnipeg, Manitoba - visiting speaker. Draculytic therapy: Lessons from the vampire bat. April 12-14, 1999.
100. American Society of Clinical Investigation, Thrombosis Advisory Group Meeting, Chicago, Illinois. April 23-25, 1999.
101. Cambridge Healthtech Institute, LaJolla, CA. Novel heparin derivatives. May 5-7, 1999.
102. Episcopal Hospital, Medical Grand Rounds, Philadelphia, PA. Low molecular weight heparin. May 27, 1999.
103. International Symposium on Thromboembolism, Lisbon, Portugal. New antithrombotic drugs: Beyond heparin and aspirin. June 4-5, 1999.
104. Congress '99, Toronto, Ontario. New anticoagulant therapies for the treatment of thrombosis. June 15, 1999.
105. Sunnybrook Cardiology Research Rounds, Toronto, Ontario. June 24, 1999.
106. XVII Congress of the International Society on Thrombosis and Haemostasis, Washington, DC. Fundamental aspects of how thrombolytics work. August 14-21, 1999.
107. University of Montreal Conference, Montreal, Quebec. Anticoagulant strategies - Beyond heparin and aspirin. September 17-18, 1999
108. Canadian Cardiovascular Society, Satellite Symposium, Quebec City. The biology of low molecular weight heparin. October 20-21, 1999.

109. Cancer Medicine and Hematology Postgraduate Course, Dana Farber Cancer Institute, Boston, Massachusetts. Anticoagulant therapy. October 24-25, 1999.
110. 65th Annual Scientific Assembly of the ACCP, Chicago, Illinois. New antithrombotic agents. November 1, 1999.
111. J. Allan Taylor International Prize in Medicine Symposium, London, Ontario. Low molecular weight heparin: The next generation. November 2, 1999.
112. American Heart Association, Atlanta, GA. Scientific foundation of antithrombin therapy. November 6, 1999.
113. Canadian Heart Research Centre Symposium, Toronto, Ontario. Update on antithrombotic therapy. November 27, 1999.
114. American Society of Hematology, Scientific Subcommittee on Thrombosis and Vascular Biology, New Orleans, Louisiana. Treatment of venous thromboembolism. Dec. 3-8, 1999.
115. JANUS III - Contemporary Cardiovascular Medicine with a View to the Future, Paradise Island, Bahamas. Mechanisms of action of new antithrombotic agents: thrombolytics IIb/IIIa inhibitors, low molecular weight heparins. January 29, 2000.
116. University of Minnesota, Minneapolis, MN. Invited speaker. February 8, 2000.
117. 6th ACCP Consensus Conference on Antithrombotic Therapy, Tucson, Arizona. New Antithrombotic Agents. February 17-19, 2000.
118. Royal College of Physicians, Davidson Lectureship, Edinburgh, Scotland. New Antithrombotic Therapies. March 10, 2000.
119. American College of Cardiology 49th Annual Scientific Session, Anaheim, California. Modern Antithrombin Therapy, March 12-15, 2000.
120. Healthcare Symposium, 2000, New York, NY. New Antithrombotics: Angiomax. April 25, 2000.
121. Practice of Evidence-based Cardiology for the Clinician - Symposium, Hamilton, Ontario. Antithrombotic and Thrombolytic Therapies in Acute Coronary Syndromes. April 27, 2000.
122. 16th International Congress of Thrombosis Satellite Symposium, Porto, Portugal. Oral Direct Thrombin Inhibition – a New Strategy in Treatment and Prophylaxis of Thrombosis – Is there a Clinical Need for a Warfarin Replacement? May 5-8, 2000.
123. Robarts Research Institute. Invited Speaker, London, Ontario. New Treatments for Unstable Angina. May 24, 2000.
124. Thrombosis – Building a New Business within AstraZeneca, Stockholm, Sweden. New Oral Anticoagulant Agents. June 8, 2000.
125. Perioperative Medicine Workshop, National Institutes of Health, Bethesda, Maryland. Perioperative antithrombotic management. June 9-10, 2000.

126. International Society of Hematology Meeting, Toronto, Ontario. New anticoagulant drugs. August 28, 2000.
127. Academic Consultant Meeting on Cardiovascular Disease, Montreal. ACS - Beyond Heparin and Aspirin. September 8-10, 2000.
128. H376/95 Advisory Board Meeting, London, UK. Are all the thrombin inhibitors the same? September 16-17, 2000.
129. Medical Grand Rounds, University of Illinois at Chicago, Chicago, IL. New therapies for unstable angina: Beyond aspirin and heparin & New anticoagulant drugs. September 28, 2000.
130. Cancer Medicine and Hematology Postgraduate Course, Harvard Medical School, Boston, MA. Anticoagulant therapy. October 16, 2000.
131. American College of Chest Physicians Satellite Symposium, San Francisco, CA. Recent advances and future directions for anticoagulation. October 23, 2000.
132. Canadian Cardiovascular Society Symposium, Vancouver, BC. Pathogenesis and treatment of unstable angina: Beyond heparin and aspirin. October 31, 2000.
133. Conference on Thromboembolic Disorders, Illinois Masonic Medical Center, Chicago, IL. New anticoagulants. November 11, 2000.
134. American Society of Hematology - Symposium, San Francisco, CA. Are all direct thrombin inhibitors the same. December 1, 2000.
135. American Society of Hematology - Education Program Session, San Francisco, CA. New anticoagulant drugs. December 2, 2000.
136. American Society of Hematology - Scientific Subcommittee, San Francisco, CA. Vascular remodeling. December 3, 2000.
137. Cardiovascular Rounds, London, Ontario. New therapies for unstable angina: Beyond heparin and aspirin. January 15, 2001.
138. American College of Cardiology Scientific Session, Orlando, Florida. Seeking an ideal agent for chronic prophylaxis. March 16, 2001.
139. American College of Cardiology Scientific Session, Orlando, Florida. Bivalirudin in PTCA: Comparison with heparin in high-risk groups. March 17, 2001.
140. American College of Cardiology Scientific Session - Brown Bag session, Orlando, Florida. Management of venous thromboembolism. March 19, 2001.
141. ACP-ASIM Annual Meeting, Atlanta, Georgia. Current concepts in venous thromboembolism. March 31 & April 1, 2001.
142. 6th National Conference on Anticoagulant Therapy, Washington, DC. Searching for the ideal anticoagulant: New anticoagulant drugs. May 11, 2001.
143. EXULT Investigators Meeting, Washington, DC. Central Adjudication. May 19, 2001.
144. XVIII Congress – ISTH Meeting, Paris, France. Satellite Symposium – Oral Direct Thrombin Inhibition – Changing Thrombosis Management, July 6-12, 2001.

145. 5th Congress of the European Association for Clinical Pharmacology and Therapeutics, Odense, Denmark. Oral Direct thrombin inhibition: the way forward in anticoagulation?, September 14, 2001.
146. A Day in Thrombosis, Mississauga, Ontario. Pathogenesis of Thrombosis, September 26, 2001.
147. Satellite Symposium, 2nd European Meeting on Vascular Biology and Medicine, Ulm, Germany. Oral Antithrombins. September 27-29, 2001.
148. New York Society for the Study of Blood, Rockefeller University, New York, New York. Draculytic therapy: lessons from the vampire bat. October 9, 2001.
149. Cancer Medicine and Hematology Postgraduate Course, Harvard Medical School, Boston, MA. Anticoagulant therapy. October 15, 2001.
150. Northern Illinois Society of Health System Pharmacists, Rockford, IL. Management of thromboembolism: a fresh look. October 23, 2001.
151. Synergy 2001 Symposium, Toronto, Ontario. New anticoagulants. November 17, 2001.
152. American Society of Hematology - Symposium, Orlando, Florida. New approaches to antithrombotic therapy, December 7, 2001.
153. Lankenau's Grand Rounds, Lankenau Hospital, Philadelphia, PA. New Anticoagulant Drugs, January 11, 2002.
154. Second Annual Rush Review Meeting, Chicago, IL. Thrombosis, February 22-23, 2002.
155. Go With The Flow: Emerging Thrombolytic Consideration, Baltimore, MD. Fragment X: How should it play into your consideration of thrombolytic therapy? April 6, 2002.
156. GIM Retreat, Niagara-on-the-Lake, Ontario. New anticoagulants, April 26-28, 2002.
157. Brigham and Women's Center of Excellence, Boston, MA. Fragment X: Implications for thrombolytic therapy, June 8, 2002.
158. SICOY/SIROT Annual Meeting, San Diego, CA. Clinical experience of direct thrombin inhibition in major orthopedic surgery, August 28, 2002.
159. Cancer Medicine and Hematology Postgraduate Course, Harvard Medical School, Boston, MA. Anticoagulant therapy. September 30, 2002.
160. 20th Annual UCLA Symposium, Santa Monica, CA. Considerations in choice of thrombolytic agents. October 2, 2002.
161. Medical Education Program, Sacramento, CA. Fragment X: Implications for thrombolytic therapy. October 3, 2002.
162. 17th International Congress on Thrombosis, Bologna, Italy. The new antithrombin agents. October 26-30, 2002.
163. 2nd Annual Day in Thrombosis, Toronto, Ontario. Pathogenesis of thrombosis and mechanism of action of antithrombotic drugs. November 2, 2002.
164. Update in Clinical Medicine, Scottsdale, AZ. Advances in the management of venous thromboembolic disease. November 4-7, 2002.

165. Montefiore Symposium, New York City, NY. Enhancing the fibrin-specificity of plasminogen activators: The importance of the (DD)E complex. November 21, 2002.
166. American Society of Hematology, Philadelphia, PA. Extending the benefits of antithrombotic therapy: new insights into patient management. December 3-8, 2002.
167. JANUS VI Meeting, Montego Bay, Jamaica. New insights into the physiology of coagulation. January 17-18, 2003.
168. CSHP Satellite Symposium, Toronto, Ontario. Overcoming barriers to extended duration of anticoagulation therapy: new antithrombins. February 5, 2003.
169. National Asociation of Inpatient Physicians Satellite Symposium, Chicago, Illinois. Prevention of DVT in the acutely ill patient. April 1, 2003.
170. Society for Vascular Medicine and Biology, 14th Annual Meeting, Chicago, Illinois. Novel agents for the management of venous thromboemboli. June 6, 2003.
171. ISTH - XIX Congress, Birmingham, United Kingdom. New oral anticoagulants. July 12-18, 2003.
172. Gordon Research Conference, New London, New Hampshire. Targets for new antithrombotic drugs. August 3-8, 2003.
173. American College of Chest Physicians - Antithrombotic Consensus Conference, Phoenix, Arizona. September 11-14, 2003.
174. Transcatheter Cardiovascular Therapeutics, 2003, Washington, DC. The pharmacology of naturally occurring and synthetic direct thrombin inhibitors and theoretical advantages. September 16-17, 2003.
175. Harvard Postgraduate Course, Boston, MA. Anticoagulant therapy. September 22, 2003.
176. 3rd Annual Day in Thrombosis, Toronto, Ontario. Pathogenesis of thrombosis and mechanism of action of antithrombotic drugs. October 8, 2003.
177. Hymie Nossel Memorial Lecture, New York, NY. Low-molecular-weight heparin, the next generation: From molecules to therapeutics. October 16, 2003.\
178. VBWG National Faculty Update Conference, Orlando, FL. New advances in anticoagulation: Oral direct thrombin inhibition. November 7, 2003.
179. American Heart Association Meeting, Orlando, FL. Treatment duration for deep vein thrombosis. November 9, 2003.
180. Visiting Speaker Seminar Series, Queen's University, Kingston, ON. Low-molecular-weight heparin: The next generation. November 25, 2003.
181. Intestinal Disease Research Program, Hamilton, ON. From concept to potential product. November, 28, 2003.
182. American Society of Hematology Meeting, San Diego, CA. Overview of anticoagulation. December 5, 2003.
183. London 2004: Current Issues Facing Coagulationists, London, UK. Thrombophilia: what to be worried about. January 11-13, 2004.

184. Blood Research Institute Lecture Series, Milwaukee, WI. Mechanisms and consequences of thrombin's interaction with fibrin. February 2-4, 2004.
185. American College of Cardiology, New Orleans, LA. Venous thrombosis: From bench to bedside. March 6-10, 2004.
186. National Hemostasis Management Consultants Group Meeting, Montego Bay, Jamaica. Meeting chairperson. March 26-28, 2004.
187. 4th International Vascular Pathology Meeting, Monte Carlo, Monaco. Melagatran and new antithrombins. June 1-6, 2004.
188. 11th International Symposium on Thromboembolism, Venice, Italy. New oral anticoagulants. June 17-19, 2004.

RESEARCH FUNDING
Independent Grants (Principal Investigator):

(a) National Institutes of Health (completed) 1984-1986
Studies of thrombosis and haemostasis . . . $190,000

(b) Heart and Stroke Foundation of Ontario (completed) 1986-1989
Biochemical indices of fibrin(ogen)olysis during tissue plasminogen activator treatment of pulmonary embolism . . . $148,000

(c) Ministry of Health of Ontario (completed) 1986-1987
Elastase activity in neonatal respiratory distress . . . $ 72,000

(d) Medical Research Council (completed) 1987-1989
Studies of neutrophil elastase . . . $113,000

(e) Heart and Stroke Foundation of Ontario (term grant) 1989-1992
Mechanism of t-PA induced fibrinogenolysis and bleeding . . . $172,000

(f) Medical Research Council (term grant) 1989-1992
Plasminogen independent and dependent interactions between plasminogen activators and fibrinogen . . . $203,500

(g) Heart and Stroke Foundation of Ontario 1992-1995
Mechanisms responsible for plasminogen activator-induced fibrin and fibrinogen proteolysis and bleeding . . . $270,400

(h) Heart and Stroke Foundation of Ontario 1992-1995
Potential clinical utility of novel antithrombin III-independent inhibitors of thrombin . . . $288,420

(i) Medical Research Council 1992-1997
Mechanism and consequences of thrombin binding to fibrin . . . $731,250

(j) Heart and Stroke Foundation of Ontario 1995-1998
Mechanisms responsible for plasminogen activator-induced fibrin and fibrinogen proteolysis and bleeding . . . $289,691

(k) Medical Research Council/CIHR 1997-2002
Methods to overcome the prothrombotic activity of thrombi . . . $694,680

(l) Heart and Stroke Foundation of Ontario 1998 -2001
Mechanism of plasminogen activator-induced bleeding . . . $311,499

(m) Heart and Stroke Foundation of Ontario 1998-2001
Improving the effectiveness of thrombolytic therapy . . . $110,622

(n) Heart and Stroke Foundation of Ontario 1999-2004
HSFO/J. Fraser Mustard Chair in Cardiovascular Research

(o) Heart and Stroke Foundation of Ontario 2001-2004
Improving the effectiveness of thrombolytic therapy . . . $301,352

(p) Heart and Stroke Foundation of Ontario 2001-2006
Mechanism of plasminogen activator-induced bleeding . . . $548,885

(q) CIHR
Canada Research Chair in Thrombosis (Tier 1) . . . $200,000/yr 2001-2008

(r) Career Investigator Award - HSFO . . . $76,250/yr 2002-2007

(s) CIHR 2002-2007
Methods to overcome the prothrombotic activity of thrombi
. . . $714,517

(t) Ontario Research and Development Challenge Fund 2002-2007
Development of new treatments for thrombosis, atherosclerosis, and osteoporosis . . . $1,000,000/yr

(u) CIHR - New Frontiers Program 2003-2004
A multidisciplinary approach to the diagnosis, prevention, and treatment of atherothrombosis . . . $67,700

(v) Heart & Stroke Foundation of Ontario 2004-2008
Improving the effectiveness of thrombolytic therapy
. . . $107,330/year

Group grants (Co-investigator):

(a) Medical Research Council (completed) 1987-1989
A randomized placebo-controlled trial of recombinant human tissue plasminogen activator in patients with deep vein thrombosis
(with J. Hirsh, A.G. Turpie, M. Gent) . . . $178,000

(b) Ministry of Health of Ontario 1987-1989
Optimal duration of oral anticoagulants in patients with deep vein thrombosis (with M. Levine, J. Hirsh) . . . $113,000

(c) Ontario Heart and Stroke Foundation 1989-1991
Effect of heparin on t-PA induced fibrin(ogen)olysis (with J. Gill)
. . . $ 66,000

(d) Ontario Heart and Stroke Foundation 1988-1992
Monitoring heparin in patients with heparin resistance
(with M. Levine, J. Hirsh) . . . $268,938

(e) Medical Research Council (Canada) 1987-1992
Basic and applied studies with low molecular weight heparin and tissue plasminogen activator (with J. Hirsh, M. Buchanan, F. Ofosu) . . . $700,000

(f) Ontario Heart and Stroke Foundation 1990-1992
Improving the efficacy of thrombolytic therapy with novel thrombin inhibitors (with P. Klement) . . . $192,900

(g) Ontario Heart and Stroke Foundation 1990-1992
Impaired fibrinolysis and recurrent venous thrombosis (with J. Hirsh) . . . $120,900

(h) Canadian Red Cross/Miles 1994-1997
Identifying the fibrin-binding site of thrombin (with Rick Austin) . . . $50,000

(i) Medical Research Council of Canada 1996-1998
Biological evaluation of radiohalogenated DNA aptamers (with Hayes Dougan) . . . $69,784

(j) Ontario Heart and Stroke Foundation 1995-1998
Mechanism of the antithrombotic effect of warfarin (with P. Klement) . . . $259,760

(k) Medical Research Council of Canada 1995-1998
Predicting and preventing recurrence of idiopathic venous thromboembolism (with C. Kearon) . . . $ 91,320

(l) CIHR 2001-2003
Markers of inflammation and thrombosis in relation to cardiovascular events in patients with acute coronary syndromes (with Shamir Mehta) . . . $118,673

PATENTS:

1. Weitz JI and Hirsh J. Methods and compositions for inhibiting thrombogenesis, patent No. 016558-00011PC, Patent Coop. Treaty, United States.

2. Weitz JI and Hirsh J. Methods and compositions for inhibitingthrombogenesis, patent No. 016558-000120US, United States.

3. Weitz JI, Hirsh J. Methods and compositions for inhibiting thrombogenesis, patent No. 016558-000150US, United States.

4. Weitz JI, Hirsh J, and Young E. Compositions and methods for inhibiting thrombogenesis, patent No. 016558-0009000GB, United Kingdom.

5. Weitz JI, Hirsh J, and Young E. Compositions and methods for inhibiting thrombogenesis, patent No. 016558-000920US, United States.

6. Weitz JI, Hirsh J, and Young E. Compositions and methods for inhibiting thrombogenesis, patent No. 016558-000930US, United States.

7. Hirsh J, Shaklee P, Knobloch J, Weitz JI. Processes for the preparation of LALMWH useful as antithrombotics, patent No. 016558-002100US, United States.

8. Austin R, Hirsh J, and Weitz J. Methods and compositions for diagnosis of hyperhomocysteinemia, patent No. 016558-001200US, United States.

9. Weitz JI and Hirsh J. Modified low molecular weight heparin that inhibits clot associated coagulation factors, patent No. 6,075,013, United States.

10. Dougan AH and Weitz JI. Extending the lifetime of anticoagulant oligodeoxynucleotide aptamers in blood, US patent No. 6,780,850 B1, United States.

11. Weitz JI and Hirsh J. Medium molecular weight heparin (MmWH) compositions that inhibit clot associated coagulation factors. PCT patent application, submitted.

12. Hirsh J, Johansen K, and Weitz JI. Antithrombotic compositions. US patent, submitted.

PUBLICATIONS
Peer reviewed:

1. Borok Z, Weitz J, Owen J, Auerbach M. and Nossel HL: Fibrinogen proteolysis and platelet α-granule release in pre-eclampsia/eclampsia. *Blood* 63:525-531, 1984.

2. Weitz JI, JA Koehn, RE Canfield, SL Landman, and R Friedman: Development of a radioimmunoassay for the fibrinogen-derived peptide Bβ1-42. *Blood* 67:1014-1022, 1986.

3. Weitz JI, SL Landman, KA Crowley, S Birken, and F Morgan: Development of a specific probe for in vivo human neutrophil elastase activity. Increased elastase activity in patients with α_1-proteinase inhibitor deficiency. *Journal of Clinical Investigation* 78:155-162, 1986.

4. Liu CY, Sobel JH, Weitz JI, Kaplan KL, Nossel HL: Immunologic identification of the cleavage products from Aα and Bβ-chains in the early stages of plasmin digestion of fibrinogen. *Thrombosis and Haemostasis* 56:100-106, 1986.

5. Weitz JI, Michelson J, Gold K, Owen J, Carpenter D: Effects of intermittent pneumatic calf compression on post-operative fibrinogen proteolysis. *Thrombosis and Haemostasis* 56:198-201, 1986.

6. Weitz JI, Crowley KA, Landman S, Lipman BI, Yu J: Increased neutrophil elastase activity in cigarette smokers. *Annals of Internal Medicine* 107:680-682, 1987.

7. Weitz J, Huang A, Landman SL, Nicholson SC, and SC Silverstein: Elastase mediated fibrinogenolysis by chemoattractant stimulated neutrophils occurs in the presence of physiologic concentrations of antiproteinases. *Journal of Experimental Medicine* 166:1836-1850, 1987.

8. Hirsh J, Buchanan M, Ofosu F, Weitz J: Evolution of Thrombosis. *Annals of the NY Academy of Sciences* 516:586-607, 1987.

9. Levy J, Pettei MJ, Weitz J: Dysfibrinogenemia in obstructive liver disease. *Journal of Pediatric Gastroenterology and Nutrition* 6:967-970, 1987.

10. Petty GW, Lennihan L, Mohr JP, Hauser WA, Weitz J, Owen J, Towey K: Complications of long-term anticoagulation in patients with stroke. *Annals of Neurology* 24:236-240, 1988.

11. Weitz J, Cruickshank M, Thong B, Levine M, Ginsberg J, Eckhardt T: Human tissue-type plasminogen activator releases fibrinopeptides A and B from fibrinogen. *Journal of Clinical Investigation* 82:1700-1707, 1988.

12. Wright S, Weitz J, Huang A, Levin S, Silverstein S, Loike J: Complement receptor type 3 (CR3, CD11b/Cd18) of human polymorphonuclear leukocytes recognizes fibrinogen. *Proceedings of the National Academy of Sciences (USA)* 85:7734-7738, 1988.

13. Kudryk B, Gidlund M, Rohoza A, Ahadi M, Coiffe D, Weitz J. Use of a synthetic homologue of human fibrinopeptide A for production of a monoclonal antibody specific for the free peptide. *Blood* 74:1036-1044, 1989.

14. O'Brodovich H, Weitz JI, Possmayer F. Effect of fibrinogen degradation products and lung ground substance in surfactant function. *Biology of the Neonate* 57:325-333, 1990.

15. Levine MN, Weitz J, Turpie AGG, Andrew M, Cruickshank M, Hirsh J. A new short infusion dosage regimen of recombinant tissue plasminogen activator in patients with venous thromboembolic disease. *Chest* 97:168-171, 1990.

16. Weitz JI, Leslie B. Urokinase has direct catalytic activity against fibrinogen and renders it less clottable by thrombin. *Journal of Clinical Investigation* 86:203-212, 1990.

17. Weitz JI, Hudoba M, Massel D, Maraganore J, Hirsh J. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III independent inhibitors. *Journal of Clinical Investigation* 86:385-391, 1990.

18. Levine MN, Hirsh J, Weitz J, Cruickshank M, Neemeh J, Turpie AGG, Gent M. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. *Chest* 98:1473-1479, 1990.

19. Cockshutt A, Weitz J, Possmayer F. Pulmonary surfactant-associated protein A enhances the surface activity of lipid extract surfactant and reverses inhibition by blood proteins in vitro. *Biochemistry* 29:8424-8429, 1990.

20. Loike JD, Sodeik B, Cao L, Leucona S, Weitz JI, Detmers PA, Wright SD, Silverstein SC. CD11c/CD18 on neutrophils recognizes a domain at the N-terminus of the Aα-chain of fibrinogen. *Proceedings of the National Academy of Sciences (USA)* 88:1044-1048, 1991.

21. Weitz JI, Leslie B, Ginsberg J. Soluble fibrin degradation products potentiate tissue plasminogen activator induced fibrinogenolysis. *Journal of Clinical Investigation* 87:1082-1090, 1991.

22. Weitz JI, Kuint J, Leslie B, Hirsh J. Standard and low molecular weight heparin have no effect on tissue plasminogen activator induced clot lysis on fibrinogenolysis. *Thrombosis and Haemostasis* 65:541-545, 1991.

23. Weitz JI. The development and application of assays for elastase-specific fibrinopeptides. *Annals of the New York Academy of Sciences* 624:154-166, 1991.

24. Nawarawong W, Wyshock E, Meloni FJ, Weitz JI, Schmaier AH. The rate of fibrinopeptide B release modulates the rate of clot formation: A study with an acquired inhibitor to fibrinopeptide B release. *British Journal of Haemoatology* 79:296-301, 1991.

25. Schmidt B, Vegh P, Weitz J, Johnston M, Caco C, Roberts R. Thrombin/antithrombin III complex formation in the neonatal respiratory distress syndrome. *American Review of Respiratory Diseases* 145:767-770, 1992.

26. Weitz JI, Silverman EK, Thong B, Campbell EJ. Plasma levels of elastase specific fibrinopeptides correlate with proteinase inhibitor phenotype: Evidence for increased elastase activity in subjects with homozygous and heterozygous deficiency of α_1-proteinase inhibitor. *Journal of Clinical Investigation* 89:766-773, 1992.

27. Weitz JI, Hirsh J. Antithrombins: their potential as antithrombotic agents. *Annual Review of Medicine* 43:9-16, 1992.

28. Demers C, Ginsberg JS, Ofosu FA, Henderson P, Weitz JI, Blajchman MA. Measurement of markers of activated coagulation in antithrombin III deficient subjects. *Thrombosis and Haemostasis* 67:542-544, 1992.

29. Klement P, Borm A, Hirsh J, Wilson G, Maraganore J, Weitz J. The effect of thrombin inhibitors on tissue plasminogen activator-mediated thrombolysis in a rat model. *Thrombosis and Haemostasis* 68:64-68, 1992.

30. Agnelli G, Renga C, Weitz JI, Nenci GG, Hirsh J. Sustained antithrombotic activity of hirudin after its plasma clearance: comparison with heparin. *Blood* 80:960-965, 1992.

31. Andrew M, Brooker L, Paes B, Weitz JI. Fibrin clot lysis by thrombolytic agents is impaired in newborns due to a low plasminogen concentration. *Thrombosis and Haemostasis* 68:325-330, 1992.

32. Rubens FD, Brash JL, Weitz JI, Kinlough-Rathbone RL. Interactions of thermally denatured fibrinogen on polyethylene with plasma proteins and platelets. *Journal of Biomedical Materials Research* 26:1651-1663, 1992.

33. Loike JD, Silverstein R, Wright SD, Weitz JI, Silverstein SC. The role of protected extracellular compartments in interactions between leukocytes, platelets, and fibrin/fibrinogen matrices. *Annals of the New York Academy of Sciences* 667:163-172, 1992.

34. Anderson DR, Lensing AWA, Wells PS, Levine MN, Weitz JI, Hirsh J. Limitations of impedance plethysmography in the diagnosis of clinically suspected deep vein thrombosis. *Annals of Internal Medicine* 118:25-30, 1993.

35. Rubens FD, Weitz JI, Brash JL, Kinlough-Rathbone RL. The effect of antithrombin III-independent thrombin inhibitors and heparin on fibrin accretion onto fibrin-coated polyethylene. *Thrombosis and Haemostasis* No. 2, 69:130-134, 1993.

36. Weitz JI, Leslie B, Hirsh J, Klement P. Alpha-2-antiplasmin supplementation inhibits tissue plasminogen activated induced fibrinogenolysis and bleeding with little effect on thrombolysis. *Journal of Clinical Investigation* 91:1343-1350, 1993.

37. Schmidt B, Vegh P, Johnston M, Andrew M, Weitz JI. Do coagulation screening tests detect inceased generation of thrombin and plasmin in sick newborn infants? *Thrombosis and Haemostasis* 69 (5), 418-421, 1993.

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40. Cosmi B, Agnelli G, Young E, Hirsh J, Weitz J. The additive effect of low molecular weight heparins on thrombin inhibition by dermatan sulfate. *Thrombosis and Haemostasis* 70:443-447, 1993.

41. Young E, Cosmi B, Weitz J, Hirsh J. Comparison of the non-specific binding of unfractionated heparin and low molecular weight heparin to plasma proteins. *Thrombosis and Haemostasis* 70:625-630, 1993.

42. Weitz JI, Hirsh J. New Anticoagulant strategies. *Journal of Laboratory and Clinical Medicine* 122:364-373, 1993.

43. Young E, Wells P, Holloway S, Weitz J, Hirsh J. Ex-vivo and in-vitro evidence that low molecular weight heparins exhibit less binding to plasma proteins than unfractionated heparin. *Thrombosis and Haemostasis* 71:300-304, 1994.

44. Levine MN, Hirsh J, Gent M, Turpie AGG, Cruickshank M, Weitz J, Anderson DR, Johnston M. A randomized trial comparing the activated thromboplastin time with the heparin assay to monitor heparin therapy in patients with acute venous thromboembolism requiring large daily doses of heparin. *Archives of Internal Medicine* 154:49-56, 1994.

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46. Weitz J. New Anticoagulant Strategies: Current Status and Future Potential. *Drugs* 48(4) 485-497, 1994.

47. Ginsberg JS, Nurmohamed MT, Gent M, MacKinnon B, Sicurella J, Brill-Edwards P, Levine MN, Panju AA, Powers P, Stevens P, Turpie AGG, Weitz JI, Buller HR, ten Cate JW, Neemeh J, Adelman B, Fox I, Maraganore J, Hirsh J. Use of hirulog in the prevention of venous thrombosis after major hip or knee surgery. *Circulation* 90:2385-2389, 1994.

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50. Wells PS, Brill-Edwards P, Stevens P, Panju A, Patel A, Douketis J, Massicotte MP, Hirsh J, Weitz J, Kearon C, Ginsberg J. A novel and rapid whole blood assay for D-dimer in patients with clinically suspected deep vein thrombosis. *Circulation* 91:2184-2187, 1995.

51. Turpie AGG, Weitz JI, Hirsh J. Advances in antithrombotic therapy: Novel agents. *Thrombosis and Haemostasis* 74(1);565-571, 1995.

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